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JAPANESE PATENT APPLICATION (A)

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A HYPOGLYCEMIC AGENT

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(72) Inventor(s): Narimitsu HONDA,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Hideaki NAGAI,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Akiko TAKISHIMA,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Akinori KAWAMURA,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Noriko OBATA,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Takashi DAN,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Masuo KOIZUMI,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.

Yasushi MURAKAMI,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Yoshikazu HINOHARA,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Hideki NAKAO,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.
Yoshio TAKAGAKI,
c/o Chugai Pharmaceutical Co. Ltd.
3-41-8 Tyaka da, Toshima-ku, Tokyo.

(71) Assignee(s): CHUGAI PHARMACEUTICAL CO. LTD.
5-5-1 Ukima, Kita-ku, Tokyo.

(74) Agent: Noriaki ANDO.

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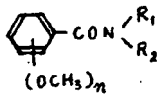
Specification

1. Title of Invention

Hypoglycaemic agent

2. Patent Claim

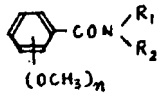
Hypoglycemic agent which has a compound represented by the following formula as the active component.



[In the formula, R_1 denotes hydrogen atom or lower alkyl group, R_2 denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

3. Detailed Description of the Invention

This invention is the invention of a hypoglycemic agent which has a compound represented by the following formula (I) as the active component



[I]

[In the formula, R_1 denotes hydrogen atom or lower alkyl group, R_2 denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

Known compounds are included in the aforesaid compound represented by the formula (I), but in the previous literature in which they are mentioned, there is no mention at all of a hypoglycemic effect or a pharmacological action suggesting this.

The compounds of this invention represented by the aforesaid formula (I) may be obtained readily by usual methods of reacting an amine compound with a methoxybenzoyl chloride compounds in the presence of a base such as triethylamine, as illustrated in the following reference example.

Reference Example

4-methoxybenzoyl chloride 17 g was added gradually under ice cooling and stirring to a mixed solution of 3-aminopyridine 9.4 g, triethylamine 15ml and acetone 200 ml. After stirring for 30 minutes at the same temperature then for 60 minutes at room temperature, the reaction solution was poured into 1 l of water, and the crystals which precipitated were collected by filtration and washed with water, then re-crystallised from methanol, to obtain 175 g of colourless acicular crystals of 4-methoxy-N-3-pyridylbenzamide (compound 1), melting point 168-170°C.

Elemental analysis	as molecular formula $C_{13}H_{12}N_2O_2$		
	C	H	N
theoretical value (%)	68.41	5.30	12.27
experimental value (%)	68.33	5.27	12.24

The compounds of Table 1 were obtained in the same way.

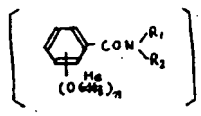


Table 1

No.	-(OMe)n	R_1	R_2	Molecular formula	Melting point (°C)	Yield (%)	Elemental anal. values Calc(%) C	H	N
							Found(%) C	H	N
2	2-OMe	H		$C_{13}H_{12}N_2O_2$	112~114	76	68.41 68.49	5.30 5.24	12.27 12.31
3	〃	〃		$C_{14}H_{14}N_2O_2$	80~82	83	69.40 69.32	5.83 5.80	11.56 11.59
4	〃	〃		$C_{15}H_{16}N_2O_2$	85~87	91	70.29 70.24	6.29 6.23	10.93 10.99
5	3-OMe	〃		$C_{13}H_{12}N_2O_2$	121~122	85	68.41 68.48	5.30 5.36	12.27 12.21
6	〃	〃		〃	155~156	83	68.41 68.43	5.30 5.31	12.27 12.30
7	〃	〃		$C_{14}H_{14}N_2O_2$	99~101	88	69.40 69.47	5.83 5.79	11.56 11.60
8	4-OMe	〃		$C_{13}H_{12}N_2O_2$	131~132	79	68.41 68.35	5.30 5.26	12.27 12.31
9	〃	〃		$C_{14}H_{14}N_2O_2$	150~153	65	69.40 69.36	5.83 5.79	11.56 11.52
10	〃	〃		〃	71~73	68	69.40 69.47	5.83 5.78	11.56 11.58
11	〃	〃		〃	61~64	77	69.40 69.45	5.83 5.88	11.56 11.63
12	〃	〃		$C_{15}H_{16}N_2O_2$	136~137	82	70.29 70.37	6.29 6.34	10.93 10.89
13	2,3-$(OMe)_2$	H		$C_{14}H_{14}N_2O_3$	117~118	58	65.10 65.14	5.46 5.49	10.85 10.91
14	〃	〃		$C_{15}H_{16}N_2O_3$	110~111	62	66.16 66.12	5.92 5.95	10.29 10.33
15	〃	〃		$C_{16}H_{18}N_2O_3$	111~112	67	67.11 67.14	6.34 6.37	9.78 9.75
16	2,4-$(OMe)_2$	〃		$C_{15}H_{16}N_2O_3$	98~99	51	66.16 66.11	5.92 5.87	10.29 10.34
17	〃	〃		〃	140~141	69	66.16 66.21	5.92 5.96	10.29 10.31
18	〃	〃		$C_{16}H_{18}N_2O_3$	93~94	63	67.11 67.15	6.34 6.39	9.78 9.74
19	2,6-$(OMe)_2$	〃		$C_{15}H_{16}N_2O_3$	155~156	67	66.16 66.22	5.92 5.97	10.29 10.24
20	〃	〃		$C_{16}H_{18}N_2O_3$	206~209	63	67.11 67.07	6.34 6.39	9.78 9.80
21	3,4-$(OMe)_2$	〃		$C_{14}H_{14}N_2O_3$	84~86	79	65.10 65.16	5.46 5.41	10.85 10.87
22	〃	〃		〃	49~51	88	65.10 65.08	5.46 5.43	10.85 10.88
23	〃	〃		$C_{15}H_{16}N_2O_3$	122~123	63	66.16 66.12	5.92 5.97	10.29 10.24
24	〃	〃		〃	128~129	74	66.16 66.19	5.92 5.88	10.29 10.33
25	〃	〃		〃	131~132	75	66.16 66.20	5.92 5.96	10.29 10.25

26	3,4-(OMe)$_2$	H		$C_{16}H_{18}N_2O_3$	69~71	63	67.11 67.15	6.34 6.37	9.78 9.77
27	〃	〃	i-Pr	$C_{12}H_{17}NO_3$	144~145	85	64.55 64.59	7.68 7.61	6.27 6.23
28	〃	〃	n-Bu	$C_{13}H_{19}NO_3$	83~84	88	65.80 65.78	8.07 8.03	5.90 5.84
29	〃	〃	s-Bu	〃	127~128	83	65.80 65.84	8.07 8.04	5.90 5.93
30	〃	〃	i-Bu	〃	124~125	80	65.80 65.85	8.07 8.11	5.90 5.95
31	〃	〃		$C_{15}H_{21}NO_3$	181~182	91	68.41 68.36	8.04 8.07	5.32 5.36
32	3,5-(OMe)$_2$	〃		$C_{18}H_{16}N_2O_3$	96~97	85	66.16 66.12	5.92 5.98	10.29 10.32
33	〃	〃		$C_{16}H_{18}N_2O_3$	119~120	87	67.11 67.18	6.34 6.37	9.78 9.72
34	3,4,5-(OMe)$_3$	〃		$C_{15}H_{16}N_2O_4$	154~156	65	62.49 62.53	5.59 5.64	9.72 9.71
35	〃	〃		〃	157~158	77	62.49 62.52	5.59 5.56	9.72 9.73
36	〃	〃		$C_{16}H_{18}N_2O_4$	115~116	58	63.56 63.52	6.00 6.04	9.27 9.25
37	〃	〃		〃	145~146	69	63.56 63.51	6.00 6.07	9.27 9.22
38	〃	〃		〃	127~128	64	63.56 63.59	6.00 6.03	9.27 9.29

39	3,4,5-(OMe)$_3$	H		$C_{17}H_{20}N_2O_4$	145~146	71	64.54 64.58	6.37 6.32	8.86 8.90
40	〃	〃	n-Pr	$C_{13}H_{19}NO_4$	114~115	73	61.64 61.60	7.56 7.59	5.53 5.57
41	〃	〃	i-Pr	〃	154~155	77	61.64 61.66	7.56 7.54	5.53 5.58
42	〃	〃	n-Bu	$C_{14}H_{21}NO_4$	133~134	80	62.90 62.87	7.92 7.86	5.24 5.27
43	〃	〃	s-Bu	〃	162~163	75	62.90 62.95	7.92 7.94	5.24 5.20
44	〃	〃	t-Bu	〃	133~134	79	62.90 62.91	7.92 7.88	5.24 5.29
45	〃	〃	i-Bu	〃	122~123	81	62.90 62.96	7.92 7.87	5.24 5.28
46	〃	〃		$C_{18}H_{23}NO_4$	182~183	88	65.51 65.54	7.90 7.93	4.78 4.72
47	〃	i-Pr	i-Pr	$C_{18}H_{25}NO_4$	127~128	72	65.06 65.11	8.53 8.59	4.74 4.71

The compounds of this invention obtained in this way have excellent hypoglycemic action, and are effective at 100 mg/kg in man, and their effect is maintained by administration of 0.1-100 mg once a day for 24 hours or more.

For administration, a preparation is used which has been formed into the desired form by a customary means normally used in drug formulation.

Example 1

5-week-old mice (male, body weight 25-30g) with 5 animals in a group were fasted for 16 hours, and then alloxan at 75 mg/kg was administered intravenously. After 48 hours, a solution or suspension of a compound of this invention (200 mg/kg) was administered orally, and after 150 minutes, blood was taken from the heart and the glucose level was measured using glucose oxidase. The measurement results are exemplified in Table 2.

Table 2

Administered compound	Blood glucose value (mg/dl) mean ± S.D.
None (control)	473 ± 28
1	326 ± 42 **
3	378 ± 31 **
4	364 ± 19 ***
6	378 ± 52 *
7	412 ± 33 *
12	383 ± 28 **
17	345 ± 41 ***
22	378 ± 37 **
25	355 ± 46 **
26	336 ± 32 ***
27	407 ± 30 *
28	402 ± 24 **
29	421 ± 27 *
32	416 ± 23 *
33	402 ± 34 *
36	416 ± 21 **
38	307 ± 43 ***
39	412 ± 31 *
41	421 ± 28 *
46	383 ± 41 **

*: P < 0.05, **: P < 0.01, ***: P < 0.001

In the Table, the compound number corresponds to the compound number of the reference examples.

Example 2

4-methoxy-N-3-pyridylbenzamide (compound 1)	100 parts
calcium hydrogen phosphate	58.5 parts
crystalline cellulose	50 parts
corn starch	40 parts
calcium stearate	1.5 parts

These components were mixed well and pressed into 250 mg tablets (content of active component 100 mg/tablet) by usual methods, for use as a hypoglycemic agent.

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